Phase I Bladder Cancer Gene Therapy

Non-Technical Abstract

Bladder cancer is the 4th most common solid tumor malignancy in men and the 5th most common overall in the United States, with an estimated prevalence of over 600,000. One form of the disease is superficial and can be treated with endoscopic resection and instillation of chemotherapy or immunotherapy drugs into the bladder to prevent recurrence. The other form is invasive cancer and is usually treated with surgery to remove the bladder and reconstruction of the urinary tract. Alternative treatment strategies for invasive cancer include combination of radiation therapy and systemic chemotherapy. These treatment strategies have significant potential morbidity, and long-term control of disease is not always complete. A novel approach to the control of cancer growth is gene therapy. Direct introduction of therapeutic genes into malignant cells may provide an effective treatment of solid tumors. Bladder cancer is uniquely suited for this type of treatment because of the ease of accessibility and direct visualization and easy sampling of bladder cells in the urine. One system is called "suicide gene therapy" and employs the introduction of the Herpes Simplex Virus thymidine kinase gene, which when expressed by the cancer cell, metabolizes the pro-drug ganciclovir, into a toxic compound that results in death of the cell. In addition, the system takes advantage of the bystander effect where the number of cells killed greatly exceeds the actual number of cells transduced by the foreign gene.

This study is designed to determine the safety of adenoviral-mediated HSV-*tk* + ganciclovir gene therapy for patients with superficial bladder cancer that have failed conventional intravesical therapy and patients scheduled to undergo radical cystectomy for invasive bladder cancer or refractory superficial disease. This treatment may provide an additional therapeutic option for patients with recurrent superficial cancer, and this treatment may provide additional benefit regarding local control and possibly a reduction in metastatic disease after definitive local therapy with cystectomy. The gene therapy will be delivered by direct injection of bladder tumors visualized via cystoscopy. Tumors will be injected with a replication defective adenovirus vector delivering the HSV-*tk* gene, and the patients will receive 14 days of intravenous ganciclovir. Patients will be hospitalized for up to 3 days for observation and initiation of ganciclovir therapy which will continue on an outpatient basis. Patients will be carefully monitored for toxic effects. Within two weeks of completing the ganciclovir therapy, patients with superficial disease will undergo an endoscopic resection of all visible tumors. Patients scheduled for cystectomy will undergo a complete removal of the bladder intended as definitive therapy for their cancer. Three to 6 patients will be tested with a low dose of the virus, and if there are no serious adverse side effects, the dose will be slowly escalated in subsequent groups of 3-6 patients until the maximum tolerated dose is achieved. Efficacy will be monitored by evidence of cell death on biopsy samples and the potential for stimulation of a local and systemic immune response. The primary objective of this initial study is to determine whether the treatment is associated with significant side effects.